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| 10/581,269 | 06/01/2006 | Stefan Arnold | LNK-009 | 3141 |

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| EXAMINER | |
|---|---|
| DEBERRY, REGINA M | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/581,269 | ARNOLD ET AL. | |
| | Examiner | Art Unit | |
| | Regina M. DeBerry | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,9,10 and 12-14* is/are rejected.

7)☒ Claim(s) *2-4,6,8 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Status of Application, Amendments and/or Claims**

The amendment and Applicant's arguments, filed 22 April 2008, have been entered in full. Claim 7 is canceled. Claims 1 and 14 are amended. Claims 1-6, 8-14 are pending and are under examination.

**Withdrawn Objections And/Or Rejections**

The rejection to claims 1 and 5 under 35 U.S.C. 102(e) as being anticipated by Canning et al., U.S. Patent No. 6,979,442 B1, as set forth at pages 3-5 of the previous Office Action (22 January 2008), is *withdrawn* in view of the amendment (22 April 2008).

The rejection to claim 12 under 35 U.S.C. 103(a) as being unpatentable over Canning et al. as applied to claim 1, and further in view of Konings et al., U.S. Patent No. 5,376,632, as set forth at pages 5-7 of the previous Office Action (22 January 2008), is *withdrawn* in view of the amendment (22 April 2008).

The rejection of claims 1-4, 6-8 and 14 under 35 U.S.C. 103(a) as being unpatentable over Canning et al., U.S. Patent No. 6,979,442 B1 in view of Williams et al., US Patent Application Publication US 2004/0022861 and Sharma et al., U.S. Patent Application US 2003/0148938 A1, as set forth at pages 7-11 of the previous Office Action (22 January 2008), is *withdrawn* in view of the amendment (22 April 2008).

The rejection to claims 1, 9-11 and 13 under 35 U.S.C. 103(a) as being unpatentable over Canning et al., U.S. Patent No. 6,979,442 B1 in view of Cho et al., U.S. Patent No. 5,656,289, as set forth at page 11 of the previous Office Action (22 January 2008), is *withdrawn* in view of the amendment (22 April 2008).

**NEW REJECTIONS/OBJECTIONS**

**Claim Rejections-35 USC § 102(b)**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogushi et al. JP 59078124 A, May 4, 1984 (abstract; translation to follow).

Ogushi et al. teach a pharmaceutical formulation comprising erythropoietin (EPO) which is adjusted to a 5-8 pH with tris (hydroxymethyl) aminomethane.

Claims 1, 5 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Espada et al. Biochemical Medicine Volume 3, pages 475-484; 1970.

Espada et al. teach a method for concentrating EPO from human urine (page 477, concentration method and description of the method). Espada et al. teach that the ethanolic solution of benzoic acid is added to the urine. The precipitate is separated and dissolved in a Tris solution (page 477, Concentration Method and Description of the Method). Espada et al. teach the Tris solution as comprising [tris (2-amino-2-hydroxymethy)-1,3-propanediol] (page 476, 2nd paragraph). Tris (2-amino-2-hydroxymethy)-1,3-propanediol is also known as tris (hydroxymethyl) aminomethane. Espada et al. teach the recovery of EPO which includes dissolving the precipitate and adjusting it at the indicated pH with the Tris solution (Table 3,

page 481). The pH includes 6.3 and 6.7. Espada et al. teach that the EPO samples were assayed in rats (page 476; Bioassay).

**Claim Rejections-35 USC § 103(a)**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ogushi et al. as applied to claim 1 above, and further in view of Konings et al. (reference of record; U.S. Patent No. 5,376,632). The teachings of Ogushi et al. et al. are described above. Ogushi et al. do not teach a pharmaceutical formulation comprising EPO and tris (hydroxymethyl) aminomethane *with* ethylenediaminetetraacetic (EDTA) acid in an amount of 0.1 to 0.5 mM. Konings et al. teach methods for stabilizing pharmaceutical compositions comprising EPO in an aqueous solution (abstract; column 4, lines 41-60). Konings et al. teach that trace amounts of heavy metal

ions catalyze the degradation of EPO, thus it may further be appropriate to add a suitable complexing agent such as calcium chloride or ethylenediaminetetraacetic acid (i.e. EDTA). Konings et al. teach that for example calcium chloride may be added at a concentration of 0.02-2 g/l (i.e. 0.1 to 0.5 mM).

It would have been obvious to one of skill in the art at the time the invention was made to modify the solution comprising EPO and tris-(hydroxymethyl)-aminomethane as taught by Ogushi et al., by formulating it with EDTA, as taught by Konings et al. with a reasonable expectation of success. The motivation and expected success is provided by Ogushi and Konings in that Ogushi et al. teach a pharmaceutical formulation comprising EPO and tris-(hydroxymethyl)-aminomethane and Konings et al. who teach the use of EDTA in formulations comprising EPO to achieve the results of reducing degradation of EPO.

Claims 9, 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ogushi et al. as applied to claim 1 above, and further in view of Cho et al. (reference of record; U.S. Patent No. 6,979,442 B1). The teachings of Ogushi et al. et al. are described above. Ogushi et al. do not teach a pharmaceutical formulation comprising EPO and tris (hydroxymethyl) aminomethane *with* 0.005-0.1 %w/v of a non-ionic detergent (polysorbate, Tween 20 or Tween 80).

Cho et al. teach pharmaceutical formulations comprising EPO and polysorbate 20 or polysorbate 80. Cho et al. teach ranges of 0.005-0.1 %w/v polysorbate 20 or polysorbate 80 (abstract; column 3, lines 22-39; column 7, line 59-column 8, line 15; column 10, lines 25-38 and column 20, lines 40-45). Polysorbate 20 and polysorbate 80, commercially branded as Tween 20

and Tween 80, respectively, are well-known in the art as polysorbates surfactants used as detergents and/or emulsifiers in pharmaceutical compositions.

It would have been obvious to one having ordinary skill in the art to combine EPO and tris (hydroxymethyl) aminomethane as taught by Ogushi et al., by formulating it with polysorbate (Tween 20 or Tween 80), as taught by Cho et al. with a reasonable expectation of success. The motivation and expected success is provided by Ogushi and Cho in that Ogushi et al. teach a pharmaceutical formulation comprising EPO and tris-(hydroxymethyl)-aminomethane and Cho et al., who teach the use of polysorbates to acts as a detergent and/or an emulsifier in pharmaceutical compositions.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Espada et al. as applied to claim 1 above, and further in view of Konings et al. (reference of record; U.S. Patent No. 5,376,632). The teachings of Espada et al. et al. are described above. Espada et al. do not teach a pharmaceutical formulation comprising EPO and tris (hydroxymethyl) aminomethane *with* ethylenediaminetetraacetic (EDTA) acid in an amount of 0.1 to 0.5 mM. Konings et al. teach methods for stabilizing pharmaceutical compositions comprising EPO in an aqueous solution (abstract; column 4, lines 41-60). Konings et al. teach that trace amounts of heavy metal ions catalyze the degradation of EPO, thus it may further be appropriate to add a suitable complexing agent such as calcium chloride or ethylenediaminetetraacetic acid (i.e. EDTA). Konings et al. teach that for example calcium chloride may be added at a concentration of 0.02-2 g/l (i.e. 0.1 to 0.5 mM).

It would have been obvious to one of skill in the art at the time the invention was made to modify the solution comprising EPO and tris-(hydroxymethyl)-aminomethane as taught by Espada et al., by formulating it with EDTA, as taught by Konings et al. with a reasonable expectation of success. The motivation and expected success is provided by Espada and Konings in that Espada et al. teach a pharmaceutical formulation comprising EPO and tris-(hydroxymethyl)-aminomethane and Konings et al. who teach the use of EDTA in compositions comprising EPO to achieve the results of reducing degradation of EPO.

Claims 9, 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Espada et al. as applied to claim 1 above, and further in view of Cho et al. (reference of record; U.S. Patent No. 6,979,442 B1). The teachings of Espada et al. are described above. Espada et al. do not teach a pharmaceutical formulation comprising EPO and tris (hydroxymethyl) aminomethane *with* 0.005-0.1 %w/v of non-ionic detergent (polysorbate, Tween 20 or Tween 80).

Cho et al. teach pharmaceutical formulations comprising EPO and polysorbate 20 or polysorbate 80. Cho et al. teach ranges of 0.005-0.1 %w/v polysorbate 20 or polysorbate 80 (abstract; column 3, lines 22-39; column 7, line 59-column 8, line 15; column 10, lines 25-38 and column 20, lines 40-45). Polysorbate 20 and polysorbate 80, commercially branded as Tween 20 and Tween 80, respectively, are well-known in the art as polysorbates surfactants used as detergents and/or emulsifiers in pharmaceutical compositions.

It would have been obvious to one having ordinary skill in the art to combine EPO and tris (hydroxymethyl) aminomethane as taught by Espada et al., by formulating it with

polysorbate (Tween 20 or Tween 80), as taught by Cho et al. with a reasonable expectation of success. The motivation and expected success is provided by Espada and Cho in that Espada et al. teach a pharmaceutical solution comprising EPO and tris-(hydroxymethyl)-aminomethane and Cho et al., who teach the use of polysorbates to acts as a detergent and/or an emulsifier in pharmaceutical compositions.

**Claim Objections**

Claims 2-4, 6, 8, and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

Claims 1, 5, 9, 10, 12-14 are rejected.

Claims 2-4, 6, 8 and 11 are objected to.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
7/14/08